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Septic shock: Past, present, and perspectives

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ABSTRACT

Septic shock remains one of the most severe complications of infection, defined by circulatory, cellular, and metabolic dysfunction and associated with persistently high mortality. The concept has evolved markedly, from early descriptions of "blood poisoning" to the recognition of sepsis as a systemic syndrome in the late 20th century. Consensus definitions and large clinical trials, including early goal-directed therapy, led to structured treatment bundles and the launch of the Surviving Sepsis Campaign, which have contributed to gradual improvements in survival.

Current management emphasizes rapid recognition, timely antimicrobials, source control, fluid resuscitation, and vasopressor support, with norepinephrine as the first-line agent. Nevertheless, significant heterogeneity among patients complicates decision-making, and debate continues around fluid thresholds, timing of vasopressor initiation, and the use of adjunctive therapies such as corticosteroids or immunomodulators.

Looking ahead, precision medicine and emerging technologies promise to refine sepsis care. Machine learning and multi-omic approaches are improving risk prediction, enabling identification of sepsis subphenotypes, and guiding individualized treatment strategies. Bedside tools assessing microcirculatory function and rapid biomarker assays may further enhance prognostication and resuscitation. Effective implementation science and rigorous validation of these tools will be critical for translating innovation into improved outcomes.

Septic shock management has advanced substantially, yet further progress requires not only personalization and innovation but also concerted efforts to reduce global disparities in access to timely diagnosis, evidence-based treatment, and long-term survivorship care.

1. Past: Historical evolution and milestones in septic shock

Septic shock has long stood as the ultimate complication of infection, recognized by profound circulatory, cellular, and metabolic disturbance with significantly increased mortality [1]. Its roots trace back to early observations of "blood poisoning," but systematic understanding was limited until the modern era. In the late 20th century, sepsis was redefined as a syndrome of dysregulated host response, not merely direct microbial invasion, recognized in the first consensus in 1991 [2]. Subsequent decades delivered pivotal milestones: refinement of definitions (Sepsis-2 in 2001, and Sepsis-3 in 2016 [1]), and the adoption of international guidelines and sepsis bundles to standardize care [3].

The Rivers trial in 2001 introduced early goal-directed therapy (EGDT), spurring widespread attention to rapid resuscitation, antibiotics, and invasive monitoring [4]. The Surviving Sepsis Campaign (SSC), launched in 2002, facilitated global guidelines and large-scale education, resulting in sepsis recognition as a time-critical medical emergency [3]. Through the 2010s, randomized trials such as ProCESS, ARISE,and ProMISe, challenged EGDT's superiority over usual care, shifting focus toward prompt recognition, bundled care, and

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individualization [5]. Meanwhile, advances in supportive management, including rational fluid therapy, vasopressor selection (notably norepinephrine), and modulation of immunologic dysregulation, incrementally improved outcomes [6].

Despite these gains, septic shock is associated with persistently high mortality, historically ranging between 40 and 50 % in severe cases [7]. Key research milestones furthered understanding of pathophysiology: microcirculatory dysfunction, mitochondrial failure, immune derangements, and the role of the endothelial glycocalyx (Fig. 1) [8]. Yet, the heterogeneity of patient populations and underlying infections contribute to treatment limitations.

One therapeutic target in patients with septic shock has been lactate clearance, as elevated lactate levels are commonly observed in the context of hypoperfusion. However, targeting lactate reduction has not consistently translated into improved outcomes, in part because lactate may also be elevated due to non-hypoperfusion mechanisms, such as the adrenergic stress response frequently associated with sepsis [9].

Several therapeutic strategies have also failed to improve outcomes in septic shock. A prominent example is recombinant activated protein C (drotrecogin alfa), which was approved in 2001 following the PROWESS trial that suggested a reduction in mortality. Subsequent systematic reviews, however, failed to confirm this benefit and highlighted an increased risk of serious bleeding, ultimately leading to its market withdrawal ten years later [10].

2. Present: Guidelines, current management, and uncertainties

The 2021 SSC guidelines underscore the urgency of septic shock care: early broad-spectrum antibiotics, intravenous crystalloids within three hours, frequent reassessment of hemodynamics, and norepinephrine as the initial vasopressor when shock persists [3]. Serum lactate is measured to gauge severity and guide resuscitation. Key current approaches include:

2.1. *Fluid resuscitation*

The systematic use of fluid responsiveness assessment using dynamic measures to guide fluid administration has been increasingly adopted over static measures. Fluid overload is now recognized to worsen outcomes by disrupting the vascular barrier and precipitating organ edema [11]. Individualized targets, with fluid responsiveness testing, are emphasized [12].

2.2. *Vasopressor therapy*

Norepinephrine is first-line, initiated early if mean arterial pressure (MAP) remains <65 mmHg after (or in parallel to) fluid resuscitation [13]. Emerging trials suggest early vasopressor initiation may mitigate fluid overload and improve outcomes, but optimal timing and

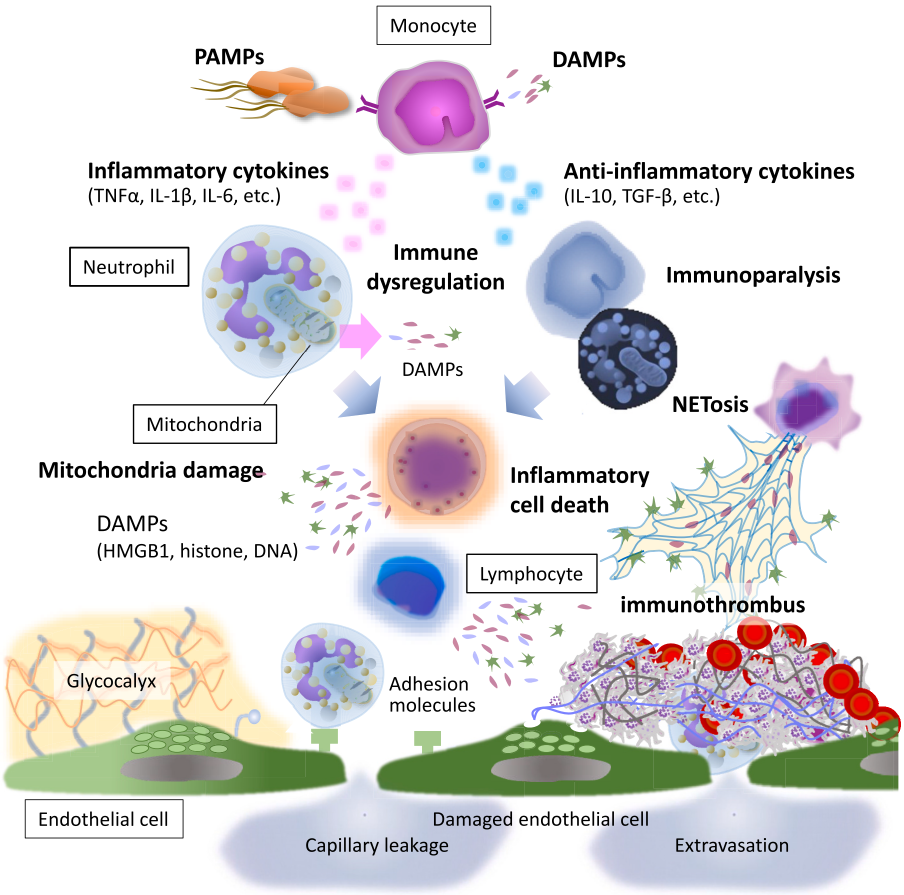

Fig. 1. Thromboinflammation in sepsis.

Schematic representation of the pathophysiological mechanisms underlying shock in sepsis. Pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) activate monocytes, and neutrophils leading to the release of inflammatory cytokines (tumor necrosis factor α [TNFα], interleukin 1β [IL-1β], IL-6) and formation of neutrophil extracellular traps (NETosis). Endothelial activation and glycocalyx injury promote adhesion molecule expression, leukocyte extravasation, and immunothrombosis. Damaged mitochondria and nuclear contents (High Mobility Group Box 1 [HMGB1], histones, and DNA) further amplify inflammation. In parallel, counter-regulatory mediators such as IL-10 and Transforming Growth Factor-β [TGF-β] contribute to immunoparalysis and immune dysregulation. The combined effects of endothelial injury, inflammatory cell death, and dysregulated host responses culminate in tissue hypoperfusion, shock, and organ dysfunction.

adjunctive agent selection (e.g., vasopressin, angiotensin II) remain uncertain [13,14].

2.3. Infection source control

Timely intervention remains critical, with delays directly correlating with mortality [3]. However, timely diagnostics remain major challenges, especially in settings with limited resources.

2.4. Adjunctive therapies

The use of corticosteroids remains controversial, though current guidelines support hydrocortisone for shock refractory to fluids and vasopressors [15]. Stress ulcer prophylaxis and glycemic control are applied selectively to avoid iatrogenic harm. The role of immunomodulators and blood purification remains unproven despite encouraging preclinical and early clinical data. Importantly, several large trials of blood purification and other adjunctive interventions have yielded negative or inconclusive results, underscoring the limitations of a "one-size-fits-all" approach. These findings highlight the urgent need for better patient phenotyping and stratification, so that therapies can be targeted to subgroups most likely to benefit. Recent perspectives, further emphasize the heterogeneity of septic shock, the promise of precision medicine, and the need to prioritize research that aligns specific therapies with defined patient subgroups [16].

2.5. Recognition of heterogeneity

Sepsis is increasingly seen as a spectrum syndrome with variable host-pathogen interactions and immune responses [17]. Risk stratification tools guide diagnosis but lack precision for individualized management [1].

Areas of uncertainty include the optimal resuscitation endpoint, optimal antibiotic administration and duration, heterogeneity of hemodynamic profiles, and the best markers for guiding therapy. Multiplicity in care settings, resource and personnel limitations, and patient factors further compound variability in outcomes.

3. Perspectives: Future directions, AI and machine learning in septic shock care

The next decade is poised for transformative changes in septic shock management, largely driven by machine learning (ML), including the integration of earlier biomarkers, multi-omics, and precision medicine.

3.1. From macrohemodynamics to microcirculatory-guided resuscitation

Hemodynamic resuscitation is expected to evolve beyond its traditional focus on macrocirculatory targets, such as blood pressure and cardiac output, toward the integration of microcirculatory assessment into routine practice. Techniques such as capillary refill time and sublingual visualization may enable real-time detection of persistent perfusion deficits that predict organ dysfunction and mortality, even after macrohemodynamic optimization. Furthermore, future research addressing the role of venous congestion as a driver of microcirculatory dysfunction could open further therapeutic alternatives [18]. Incorporating these tools into resuscitation algorithms could allow for more precise, individualized interventions, help prevent overtreatment, and ultimately improve outcomes in patients with septic shock [19,20].

3.2. AI and machine learning

ML models, leveraging vast electronic health record (EHR) data, already outperform clinical scoring systems in early sepsis and septic shock prediction, with some reporting AUROCs >0.9 [21,22]. These systems are expanding to automate risk stratification, predict hemodynamic deterioration, simulate fluid/vasopressor responsiveness or optimize second-line vasopressors [23]. The integration of structured and unstructured EHR data allows continuous real-time risk assessment, potentially triggering earlier and more personalized interventions. The real-world barriers such as high costs, external validation of machine learning tools, and the training needed for bedside integration are challenging to fully implement these strategies.

3.3. Precision phenotyping and dynamic decision-support

ML-aided clustering of patient data is uncovering subphenotypes ("hyperinflammatory," "immunoparalytic") that may guide tailored therapy beyond one-size-fits-all approaches [17,24]. Multi-omic analyses, such as transcriptomics, metabolomics, proteomics, promise to identify new therapeutic targets for the development of new potential drugs [25].

Bedside ML tools may soon help triage patients, recommend interventions, and predict complications (e.g., acute kidney injury, acute respiratory distress syndrome - ARDS), continuously updating as new data emerge [22,24].

3.4. Novel therapeutics and biomarkers

With the aid of computational modelling, the rapid validation of candidate pathways, biomarkers, and therapeutic targets is becoming increasingly feasible. Systems biology and multi-omics integration (genomics, transcriptomics, proteomics, and metabolomics) provide unprecedented insights into the host response to infection, enabling the identification of endotypes that may respond differently to specific interventions. In parallel, advances in machine learning are accelerating the discovery and validation of predictive signatures, supporting the shift toward precision medicine in sepsis.

At the clinical level, efforts are underway to develop rapid bedside assays for immune profiling, endothelial function, and organ dysfunction, which could enable near–real-time assessment of disease trajectory. Point-of-care biomarkers are beginning to revolutionize the early diagnosis of sepsis, as well as bedside risk stratification and prognostication. Combining these diagnostic tools with AI-driven decision support systems holds the promise of guiding timely, individualized therapeutic strategies, ultimately improving patient outcomes [26].

3.5. Implementation science

The translation of research advances to bedside practice remains challenging. ML tools will need rigorous external validation, transparency, and workflow integration to avoid alert fatigue and disparities in care [22].

Preventing and treating the long-term consequences of septic shock in survivors is becoming ever more important as acute mortality declines. Approximately half of patients survive septic shock, yet many develop lasting complications including cardiovascular disease, chronic kidney disease, neurocognitive impairment, and functional disability. For instance, Shankar-Hari et al. followed nearly 95,000 sepsis survivors across England and found that age, comorbid burden, and organ dysfunction known at index hospitalization were strongly associated with elevated mortality for up to 5–6 years post-discharge [27]. More recently, Malomo et al. demonstrated that structural cardiac changes (left ventricular dilation, elevated myocardial T1) persist weeks after sepsis in UK survivors, suggesting ongoing risk to cardiovascular health [28].

Addressing these long-term outcomes requires systematic follow-up, better rehabilitation pathways, and integration of chronic disease prevention into sepsis survivorship care plans. International collaboration and high-quality, longitudinal datasets will be essential to characterise the trajectories of survivorship, identify modifiable risk factors, and evaluate interventions spanning from acute care through extended recovery. Ultimately, a comprehensive strategy is needed to reduce the full burden of sepsis, both immediately and in the long term.

4. Conclusions

Septic shock management has progressed from inflammation-centered models to evidence-based, protocol-driven approaches that incorporate hemodynamic optimization and early interventions. Despite these advances, considerable uncertainty persists due to patient heterogeneity and variability in treatment responses. The future of care lies in precision medicine, with artificial intelligence and machine learning offering the potential to individualize treatment, enhance early detection and prognostication, and refine therapeutic strategies. Successfully bridging innovation with clinical implementation will be essential to improving outcomes in septic shock.

CRediT authorship contribution statement

Erika P. Plata-Menchaca: Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Orlando Rubén Pérez-Nieto:** Writing – original draft, Investigation, Conceptualization. **Eduardo Kattan:** Supervision, Project administration, Investigation, Data curation. **Toshiaki Iba:** Writing – original draft, Validation, Investigation, Conceptualization. **Ricard Ferrer:** Validation, Supervision, Investigation, Conceptualization.

Author statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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